

REMARKS

This Response, filed in reply to the Office Action dated October 12, 2007, is believed to be fully responsive to each point of objection and rejection raised therein. Accordingly, favorable reconsideration on the merits is respectfully requested.

Claims 1-20 are all the claims currently pending in the application, of which Claims 11-20 are withdrawn from consideration as being directed to nonelected inventions. Claims 1-10, are rejected. Claims 1-4 and 8 are currently amended and entry of these amendments is respectfully requested. Support for these amendments can be found throughout the specification, and at least at the following. Support for the amendment to Claim 1 can be found in lines 11-12 of paragraph [0032] of the published specification, support for the amendment to Claim 2 can be found in lines 7-9 of paragraph [0033] of the published specification, support for the amendment to Claim 3 can be found in lines 13-16 of paragraph [0033] of the published specification and support for the amendment to Claim 4 can be found in lines 14-16 of paragraph [0078] of the published specification. Upon entry of these amendments, Claims 1-20 will be pending in the Application.

Information Disclosure Statements

Applicants thank the Examiner for returning signed and initialed copies of the PTO Forms SB/08 that accompanied the Information Disclosure Statements filed March 23, 2005 and December 21, 2005.

Claims 1-4 are Not Indefinite Under 35 U.S.C. § 112

On page 2 of the Office Action, Claims 1-4 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

Specifically, the Office alleges that Claims 1 and 2 are indefinite because it is unclear if iturin A is externally added to the medium, or if it is produced by the microorganism. In addition, the Office alleges that “mass %” is unclear.

Applicants respectfully submit that Claims 1 and 2 as originally presented are not indefinite in view of the guidance and the working examples provided in the specification. Nevertheless, without acquiescing in the rejection, and solely to advance prosecution, Applicants hereby amend Claim 1 to recite that the *Bacillus* microbes produce iturin A, and homologues thereof. Further, to even further clarify Applicants’ claimed invention, the relevant claims have been amended to recite “% mass” rather than “mass%.” Applicants respectfully submit that the amendments to the claims overcome the rejection.

The Office further alleges that Claim 3 is indefinite in recitation of the phrase “substantially no ability to produce surfactin” because this statement does not define whether the claim encompasses bacteria that do not inherently produce surfactin, or those that have been modified so as to not produce surfactin, for example by recombinant DNA techniques.

Applicants respectfully submit that Claim 3 as originally presented is not indefinite under 35 U.S.C. §112. Specifically, Applicants respectfully disagree that Claim 3 is rendered indefinite because the claim does not explicitly recite how these *Bacillus* strains are derived. Applicants respectfully submit that one of ordinary skill in the art would understand that the *Bacillus* strains encompassed by Claim 3 may include naturally occurring strains known to produce little surfactin, in addition to engineered strains produced through a variety of

techniques well known in the art, such as random or targeted mutagenesis, and selected according to the desired phenotype, namely a reduction in, or absence of, surfactin production. Nevertheless, to even further clarify Applicants' claimed invention, Applicants hereby amend Claim 3 to recite "wherein the *Bacillus* microbe having an ability to produce iturin A and its homologues is a *Bacillus* microbe that produces 50ppm or less of surfactin in the medium during *Bacillus* microbe cultivation."

On page 4 of the Office Action, Claim 4 is rejected as being indefinite because recitation of "in terms of K_2HPO_4 " is unclear since K_2HPO_4 can allegedly refer to stoichiometric phosphate equivalents, or simply to the salt of di-potassium monohydrogen phosphate itself.

To further clarify Applicants' claimed invention, Applicants hereby amend Claim 4 to mandate that the medium for *Bacillus* microbe cultivation contains 3% mass, or less, of K_2HPO_4 . Applicants respectfully submit that the amendment to the claim overcomes the rejection.

Withdrawal of the indefiniteness rejections is respectfully requested.

Claims 1-10 are Not Obvious Under 35 U.S.C. § 103

On page 3 of the Office Action, Claims 1-10 are rejected under 35 U.S.C. §103(a) as being unpatentable over Phae *et al.* (*J. of Fermentation and Bioengineering*, 1991) in view of Tanaka *et al.* (U.S. Patent No. 5,470,827).

The Office alleges that Phae *et al.* disclose a *Bacillus subtilis* strain that produces and accumulates iturin A and its homologues in a liquid medium containing glucose, polypeptone and K_2HPO_4 . Further, the Office asserts that Phae *et al.* do not mention the production of surfactin in the culture. The Office admits that Phae *et al.* do not disclose a yield of 1.5 g/L or greater, but alleges that since Phae *et al.* perform the steps of the claimed method, it would be

obvious though mere routine optimization of reaction time, temperature and microbe concentration, to meet this limitation.

Further, the Office admits that Phae *et al.* do not disclose the specific cell lines of *Bacillus subtilis* recited in Claims 6 and 7. In an attempt to rectify this deficiency, the Office refers to M.P.E.P. § 2144.09, where it is stated that “[a] *prima facie* case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities.” The Office alleges that in the absence of any evidence to the contrary, one of ordinary skill in the art would expect the same results for the *Bacillus subtilis* used by Phae *et al.* and the strains used by Applicants.

Further still, the Office acknowledges that Phae *et al.* do not disclose the use of soybean powder, or its extract, to cultivate the *Bacillus* microbes. However, the Office alleges that it would have been obvious to use soybean powder, or extract, in view of the disclosures of Tanaka *et al.* In this regard, the Office asserts that Tanaka *et al.* disclose a method for cultivating *Bacillus* strains in glucose and that soybean meal can be substituted for glucose in a medium that contains potassium phosphate. The Office also alleges that the iturin A accumulated in the culture is isolated by Tanaka *et al.* and dried under a vacuum.

From these two references, the Office concludes that it would have been obvious for one of ordinary skill in the art to combine the teachings of Phae *et al.* with Tanaka *et al.* to arrive at the claimed invention. The Office asserts that Tanaka *et al.* disclose that *Bacillus subtilis* produces iturin A, thus providing a motivation and a reasonable expectation of success in combining the teachings of Tanaka *et al.* to add soybean meal to the culture medium of that disclosed by Phae *et al.*

Applicants traverse the rejection, and respectfully submit that the combination of Phae *et al.* and Tanaka *et al.* is insufficient to render the claimed invention obvious in view of the following remarks.

First, the Office alleges that while Phae *et al.* do not disclose the particular yield of 1.5g/L of iturin A, it would take mere routine optimization of reaction time and temperature as well as microbe concentration to meet such a limitation. However, Applicants respectfully submit that neither the state of the art, nor the cited references, would lead one of ordinary skill in the art to surmise that optimization of these variables could result in such a drastic increase in iturin A production. Indeed, the only variable that Phae *et al.* suggest may have an effect is reaction temperature. However, Phae *et al.* already undertake optimization of this variable and conclude that “30°C was optimal in the production of iturin” (page 120, column 1, lines 18-19).

With regard to reaction time, Phae *et al.* also disclose, in Figures 2 and 10 for example, monitoring iturin A production over time until the concentration of iturin A in the medium reaches saturation. Specifically, iturin A concentration reaches a plateau by 80 hours, at which time the concentration of iturin in the medium is merely 620 mg/L. Therefore, one of ordinary skill in the art would conclude that the method of iturin production disclosed by Phae *et al.* is already optimized with regard to reaction time, and is unlikely to be capable to producing iturin A in the medium to a concentration of 1.5 g/L, even if the reaction time is extended. Thus, in view of the data proffered by Phae *et al.*, one of ordinary skill in the art would not expect reaction time could be optimized in such a way as to produce a drastic increase in iturin A production, since maximal yield occurred at the plateau phase.

Further, pursuant to M.P.E.P. §2144.09, temperature, time and microbe concentration must be known to be result-effective variables before their optimization can be used to support a

case of obviousness. In view of the experiments of Phae *et al.*, Applicants respectfully submit that the Office has failed to meet its burden in demonstrating reaction time and microbe concentration are result-effective variables when producing iturin A at a concentration of 1.5g/L or more.

Further, with regard to Claims 6 and 7, the Office alleges that Phae *et al.* do not disclose the specific strains of *B. subtilis*. In an attempt to rectify this deficiency, the Office refers to M.P.E.P. § 2144.09, stating that “a *prima facie* case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities.” However, Applicants respectfully point out that the section of the M.P.E.P. cited by the Examiner is exclusively directed to chemical compounds, namely “homologs, analogues [and] isomers.” One of skill in the art would appreciate that *Bacillus* species are not chemical compounds, but rather, are complex prokaryotes. Accordingly, the technical and legal basis for rejection of Claims 6 and 7 is clearly improper.

Further still, the Office alleges that Phae *et al.* disclose the claimed invention, except for the use of soybean powder or its extract to cultivate the *Bacillus* microbes. In this regard, the Office refers to Tanaka *et al.*, who allegedly disclose “a method of cultivating *Bacillus* in glucose [but also that] soybean meal can be substituted for glucose as well in a medium that contains potassium phosphate.” Initially, Applicants respectfully point out that Tanaka *et al.* do not use soybean meal as a substitute for glucose (a carbon source), but rather, it is used as a nitrogen source. Further, Applicants respectfully submit that the combination of Phae *et al.* and Tanaka *et al.* fail to render the claimed invention obvious due to the unexpectedly superior results obtained by Applicants when soybean powder or soybean extract is used, versus other nitrogen sources commonly used in the art.

In this regard, Applicants respectfully submit that although Tanaka *et al.* disclose that soybean meal may be used as a nitrogen source for iturin A-producing microbes, Tanaka *et al.* do not even suggest which of the nitrogen sources listed may be preferable over the others. Thus, one of skill in the art would have no obvious reason to favor soybeans as a nitrogen source over the other compounds listed. However, in Example 1 of Applicants' specification, different nitrogen sources are directly compared, including soybean powder and peptone (used in the reactions of Phae *et al.* and Tanaka *et al.*) for their effect on iturin A production. The results in Example 1 clearly demonstrate that the use of soybean powder results in the production of an unexpectedly high concentration of iturin A and its homologues. Indeed, since soybean powder is used as a nitrogen source for bacterial growth, as is acknowledged by Tanaka *et al.*, Applicants respectfully submit that this result is clearly unexpected because one of ordinary skill in the art would be unable to predict, and would have no expectation, that the nitrogen source component of the growth medium could influence iturin A production to such a degree. Indeed, when compared to peptone, the use of soybean powder resulted in a 10-fold increase in iturin A production, even when the same % mass of peptone and soybean powder were used (as shown in Example 1). In addition, neither the cited references, nor the art itself, even suggests that the choice of nitrogen source may influence iturin A yield, let alone suggest that soybean meal may be used to increase iturin production by the magnitude demonstrated by Applicants. In this regard, although Tanaka *et al.* describes numerous materials useful as nitrogen sources, including soybean meal, all of the examples proffered by Tanaka *et al.* use either yeast extract (0.1%) or peptone (0.5%). In such cases, the maximum amount of iturin A obtained from 15 L of the medium was only 597 mg, which corresponds to a concentration of only 40 mg/L. At no point

do Tanaka *et al.* even suggest that substitution with a different nitrogen source may improve yield, let alone suggest that soybean meal in particular may improve yield.

Thus, in view of the unexpectedly high concentrations of iturin A produced when using soybean meal as a nitrogen source for the growth of iturin A-producing *Bacillus* species, and the lack of any teaching or suggestion within the cited references or within the art itself that such an effect could be predicted, one of ordinary skill in the art would have no reason to suspect that the use of a different nitrogen source, let alone soybean powder, would significantly increase iturin A yield. In view of the foregoing, Applicants respectfully submit that the cited references do not render Applicants' claimed invention obvious.

Duty of Disclosure

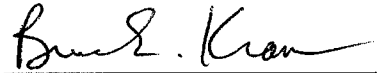
On page 5 of the Office Action, the Office requests that Applicants provide a list of all copending U.S. applications that set forth similar subject matter to the present claims and a copy of the claims of any copending applications, in the response to the Office action.

Applicants respectfully submit that although they have a duty to disclose information material to patentability, pursuant to M.P.E.P § 2001.06(b) it is not Applicants' burden to furnish the Examiner with a complete copy of the claims of each copending application.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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